UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

December 10, 2015

Subject: SPC4 Plus 1
EPA File Symbol: 2517-RTT
DP Barcode 430473
Action Code: R314
PC Codes: 097805 (Deltamethrin: 4%)
129032 (Pyriproxyfen: 1%)

From: Byron T. Backus, Ph.D., Toxicologist
CITAB
Registration Division (7505P)

Byron T. Backus
Dec. 10, 2015
JCR

Through: John Redden, M.S., Senior Risk Assessor
CITAB
Registration Division (7505P)

To: Timothy Ciarlo/Kable Davis, RM 03
IVB1
Registration Division (7505P)

Applicant: SERGEANT'S PET CARE PRODUCTS, INC.

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt.
Deltamethrin:	4.00%
Pyriproxyfen	1.00%
Inert Ingredients:	95.00%
Total	100.00%

BACKGROUND: This product is a dog collar with a 12-month claim for fleas and 6-month claim for ticks. From the bean sheet for this application: "Please review the cited acute tox data for 2517-RTT and determine if they are acceptable for product registration."

COMMENTS AND RECOMMENDATIONS:

1. According to the data matrix (dated 8/04/2015) the registrant has cited two sets of data for the acute toxicity data requirements (essentially a bridging argument): the first set includes MRIDs 42889001 (acute oral LD_{50}), 42889002 (acute dermal LD_{50}), 42889003 (primary eye irritation), 42889004 (primary dermal irritation), 42889005 (dermal sensitization); the second set (submitted by Sergeant's Pet Care Products, Inc.) contains MRIDs 43856502 (acute oral LD_{50}), 43856503 (acute dermal LD_{50}), 43856504 (primary eye irritation), 43856504 (primary dermal irritation), and 43856506 (dermal sensitization).

2. The registrant has addressed the acute inhalation toxicity data requirement with a waiver request (MRID 49211401), stating that the active ingredients are nonvolatile and are incorporated into the collar from which they are slowly released. Based on the registrant's arguments, as well as the nature of this type of product, CITAB concludes that an acute inhalation study is not necessary and can be waived, with assignment to toxicity category IV by this exposure route.

3. The studies in MRIDs 428890-01 through -05 were originally submitted by Roussel-Uclaf Corporation to support EPA File Symbol 432-TTO, a dog collar containing 4% deltamethrin as the only active ingredient. According to OPPIN, 432-TTO was transferred (without being registered?) on March 23, 1995 to 68451-R, which was registered under 68451-1 on June 5, 1996.

4. The studies in MRIDs 428890-01 through -05 were reviewed (TXR 5014801, May 16, 1995) by PRS, and were all classified as acceptable. The following is the acute toxicity profile for 68451-1 (a collar with 4% deltamethrin as sole active ingredient) based on the results of these studies (with a waiver for the inhalation study):

Oral LD_{50} (rat)	Acceptable	Tox. Cat. III	MRID 42889001
Dermal LD_{50} (rabbit)	Acceptable	Tox. Cat. III	MRID 42889002
Inhalation LC_{50} (rat)	Waived	Tox. Cat. IV	-
Primary Eye Irritation (rabbit)	Acceptable	Tox. Cat. III	MRID 42889003
Primary Dermal Irrit. (rabbit)	Acceptable	Tox. Cat. IV	MRID 42889004
Dermal Sensitization (guinea pig)	Acceptable	Not a sensitizer	MRID 42889005

5. There is no record that the studies in MRIDs 438565-02 through -06 were ever reviewed. According to OPPIN these studies were submitted to support EPA Reg. No. 2517-109. CITAB has now reviewed these studies (DER attached) and has determined that four of the studies (MRIDs 438565-03 through -06) are acceptable. The oral LD_{50} study (MRID 43856502) has been classified as unacceptable (the test material that was administered to the rats was an extract prepared by incubating 20 g of the ground test substance in 40 mL saline at 70°C for 24 hrs and then decanting the cooled supernatant fluid. The study has been classified as unacceptable because the test material [presumably the supernatant fluid] was not analyzed for pyriproxyfen content, so it is not known what the dosage was in terms of this active ingredient, or whether the rats were even exposed to it). However, pyriproxyfen is

known to be relatively nontoxic to mammalian species, and there are a number of acute oral LD_{50} studies demonstrating this. **The registrant should cite an acceptable oral LD_{50} study on a formulation containing >2% pyriproxyfen that demonstrates toxicity category III or (preferably) IV by this exposure route.**

6. Based on the results of the studies in MRIDs 438565-03 through -06, and with assignment of the collar to toxicity category IV by the oral exposure route, the following is the acute toxicity profile for a 2% pyriproxyfen collar:

Oral LD_{50} (rat)	*	Tox. Cat. IV	*
Dermal LD_{50} (rabbit)	Acceptable	Tox. Cat. III	MRID 43856503
Inhalation LC_{50} (rat)	Waived	Tox. Cat. IV	-
Primary Eye Irritation (rabbit)	Acceptable	Tox. Cat. III	MRID 43856505
Primary Dermal Irrit. (rabbit)	Acceptable	Tox. Cat. IV	MRID 43856504
Dermal Sensitization (guinea pig)	Acceptable	Not a sensitizer	MRID 43856506

*Oral LD_{50} study in MRID 43856502 has been classified as unacceptable; the registrant should cite an acceptable oral LD_{50} study conducted on a formulation containing >2% pyriproxyfen demonstrating toxicity category III or (preferably) IV by this exposure route.

7. The following is the acute toxicity profile for 2517-RTT, based on a bridging of the two sets of cited acute toxicity studies (assuming an acceptable oral LD_{50} study for pyriproxyfen is cited) :

Oral LD_{50} (rat)	Bridged	Tox. Cat. III
Dermal LD_{50} (rabbit)	Bridged	Tox. Cat. III
Inhalation LC_{50} (rat)	Waived	Tox. Cat. IV
Primary Eye Irritation (rabbit)	Bridged	Tox. Cat. III
Primary Dermal Irrit. (rabbit)	Bridged	Tox. Cat. IV
Dermal Sensitization	Bridged	Negative

8. Based on the acute toxicity profile above, the following is the precautionary and first aid labeling for EPA File Symbol 2517-RTT, as obtained from the Label Review System:

PRODUCT ID #: **002517-00177**

PRODUCT NAME: **SPCP4 Plus 1**

PRECAUTIONARY STATEMENTS

SIGNAL WORD: **CAUTION**

Hazards to Humans and Domestic Animals:

Harmful if absorbed through skin. Harmful if swallowed. Causes moderate eye irritation. Avoid contact with skin, eyes or clothing. Wash thoroughly with soap and water after handling.

First Aid:

If on skin:
-Take off contaminated clothing.
-Rinse skin immediately with plenty of water for 15-20 minutes.
-Call a poison control center or doctor for treatment advice.

If swallowed:
-Call a poison control center or doctor immediately for treatment advice.
-Have person sip a glass of water if able to swallow.
-Do not induce vomiting unless told to by a poison control center or doctor.
-Do not give anything to an unconscious person.

If in eyes:
-Hold eye open and rinse slowly and gently with water for 15-20 minutes.
-Remove contact lenses, if present, after the first 5 minutes, then continue rinsing.
-Call a poison control center or doctor for treatment advice.

Have the product container or label with you when calling a poison control center or doctor or going for treatment. You may also contact 1-800-xxx-xxxx for emergency medical treatment information.

9. The proposed precautionary labeling and first aid statements as proposed by the registrant are acceptable.

10. The statement: "Do not use on puppies under 12 weeks. Do not use on cats. Consult a veterinarian before using this product on debilitated, aged, pregnant, medicated, or nursing animals. Sensitivities may occur after using ANY pesticide product for pets. If signs of sensitivity occur, remove collar and bathe your dog with mild soap and rinse with large amounts of water. If signs continue, consult a veterinarian immediately." is consistent with PR Notice 96-6 and is acceptable

11. With the indicated revision in the data matrix for the acute oral LD_{50} study with pyriproxyfen, the acute toxicity data requirements for the registration of EPA File Symbol 2517-RTT will have been satisfied.

12. This memorandum addresses only the acute toxicity data requirements for 2517-RTT; the companion animal safety data requirements will be addressed in a separate memorandum.

Reviewer: Byron T. Backus, Ph.D.
Date: December 10, 2015
Risk Manager (EPA): 03

The following is the Acute Toxicity Data Evaluation Record (DER) for the five acute toxicity studies (MRIDs 43856502 through 43856506) cited to support EPA File Symbol 2517-RTT (originally submitted to support 2517-109):

1. DP BARCODE: 430473				
2. PC CODE: 129032 (Pyriproxyfen: 2%)				
3. CURRENT DATE: December 10, 2015				
4. TEST MATERIAL: Ground 2% Pyriproxyfen Collar; Lot/Batch No. LC-4080; described (page 10 of MRID 43856503) as large reddish granules.				
Study/Species/Lab Study # /Date	**MRID**	**Results**	**Tox Cat**	**Core Grade**
Acute oral toxicity / rat / Cosmopolitan Safety Evaluation, Inc., Lafayette, NJ / Study #A3414 / November 22, 1994 / OCSPP 870.1100; OECD 401	43856502	The test material was an extract prepared by incubating 20 g of the ground test substance in 40 mL normal saline at 70°C for 24 hrs and then decanting the cooled supernatant fluid. 5M & 5F fasted Sprague-Dawley derived rats were dosed with 10 mL/kg of this fluid. There was no mortality and there were no signs of toxicity. All rats gained weight days 0-7 and again days 7-14. There were no abnormalities at gross necropsy. The study is classified as Unacceptable because the test material (the supernatant fluid) was not analyzed for pyriproxyfen content, so it is not known what the dosage was in terms of this active ingredient.	-	U
Acute dermal toxicity / rabbit / Cosmopolitan Safety Evaluation, Inc., Lafayette, NJ / Study #B3414 / November 22, 1994 / OCSPP 870.1200; OECD 402	43856503	The test material, ground 2% Pyri-proxyfen collar, was applied to 5M & 5F albino rabbits at 2010 mg/kg with 24-hr occluded dermal exposure. Individual doses ranged from 5.4 to 6.8 g; each individual dose was moistened with ~4 mL distilled water. There was no mortality and there were no signs of toxicity. At 24 hrs there was grade 1 erythema in 4/5M & 2/5F. All rabbits gained weight days 0-7 and again days 7-14. There were no abnormalities at gross necropsy. Dermal LD_{50} > 2010 mg/kg.	III	A

Primary eye irritation / rabbit / Cosmopolitan Safety Evaluation, Inc., Lafayette, NJ / Study No. D3414 / November 22, 1994 / OCSPP 870.2400; OECD 405	43856505	0.1 g was instilled in one eye of each of 6 rabbits. At 1 hour 2 eyes scored "1" for iritis. At 24 hrs 1/6 eyes scored "1" for iritis and 5/6 scored "1" for redness and/or chemosis. All scores were zero by day 4.	III	A
Primary dermal irritation / rabbit / Cosmopolitan Safety Evaluation, Inc., Lafayette, NJ / Study No. E3414 / November 22, 1994 / OCSPP 870.2500; OECD 404	43856504	0.5 g of test substance (2% Pyriproxyfen collar ground), moistened with 0.3 mL distilled water ("The maximum amount of water to allow even dispersion. The plastic did not become 'pasty'") was applied per application site on each of 6 rabbits, with 4-hour occluded exposure. At ~45 minutes following exposure one site scored 1 for erythema; all other scores were zero. All scores were zero at 24, 48 & 72 hrs. Primary dermal irritation score reported as 0.2 (this reviewer calculates it as 0.04).	IV	A
Dermal sensitization / guinea pig / Cosmopolitan Safety Evaluation, Inc., Lafayette, NJ / Study No. F3414 / November 22, 1994 / OCSPP 870.2600; OECD 406	43856506	Buehler method: for induction 3 once-a-week 6-hr exposures to 0.5 g of the test substance + 0.3 mL distilled water to 10 guinea pigs. Challenge was to 0.5 g test material + 0.3 mL distilled water at a new site; at challenge a group of 5 naïve guinea pigs was similarly tested. Highest score during induction and challenge was ± (defined as slight, patchy erythema, barely perceptible or questionable, but not an indication of sensitization). This score (±) was present in 2/10 previously induced and 2/5 naïve animals at 24 hrs after challenge; all scores were zero at 48 & 72 hrs. Historical positive control (0.1 mL 20% w/w p-phenylenediamine dihydrochloride in distilled water for induction and challenge) resulted in a positive response in 10/10 induced and 0/5 naïve guinea pigs.	Negative	A

n.d. = not determined; Core Grade Key: A =Acceptable, S = Supplementary, W = Waived, U = Unacceptable, D = Data Gap